

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 31/70	A1	(11) International Publication Number: WO 98/52576 (43) International Publication Date: 26 November 1998 (26.11.98)
(21) International Application Number: PCT/EP98/03175 (22) International Filing Date: 22 May 1998 (22.05.98) (30) Priority Data: 97201513.5 21 May 1997 (21.05.97) EP (34) Countries for which the regional or international application was filed: NL et al. (71) Applicant (for all designated States except US): NEW KEY FOODS N.V. [BE/BE]; Volhardingstraat 29, B-2650 Edegem (BE). (72) Inventor; and (75) Inventor/Applicant (for US only): VANDEN BERGHE, Dirk, Andre, Richard [BE/BE]; Heirweg 154, B-9270 Laarne (BE). (74) Agent: VAN SOMEREN, Petronella, Francisca, Hendrika, Maria; Arnold & Siedsma, Sweelinckplein 1, NL-2517 GK The Hague (NL).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: USE OF GLUCOSAMINE AND GLUCOSAMINE DERIVATIVES FOR QUICK ALLEVIATION OF ITCHING OR LOCALIZED PAIN (57) Abstract The present invention relates to the new use of glucosamine and/or its derivatives for the preparation of a therapeutical composition for treating and quick relief of itching and/or local pain which results from a variety of causes. The invention further relates to therapeutical compositions for use in this treatment.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

**USE OF GLUCOSAMINE AND GLUCOSAMINE DERIVATIVES
FOR QUICK ALLEVIATION OF ITCHING OR LOCALIZED PAIN**

Field of Invention

The invention relates to the preparation of a topical medication for very quick alleviation and relief of itching and/or localized pain caused by a wide range of medical indications.

5

Background of the invention

Itching (pruritus) has a lot of underlying causes and can lead to a lot of complications by scratching. Itching may be associated with local pain.
10 Pain can also occur independently. Both local pain and itching comprise the sensation associated with a lot of causes: inflammation, dry skin, infection by micro-organisms such as bacteria, fungi and viruses, corns, wounds, ulcers, stings, insect bites, allergic reactions,
15 hyper proliferation of the epithelial layer, different types of treatment with chemicals, affecting the skin, eczema, etc. But there is also local pain associated with other affections, such as tendinitis, rheumatism and rheumatic affections, such as reumatalgia, reumatide,
20 reumatismus articulorum acutus, reumatismus articulorum chronicus, reumatismus musculorum, reumatismus nervosum, reumatismus nodosum, rheumatoid affections, different kinds of arthritis such as arthritis urica, arthritis acuta, arthritis sicca, arthritis hyperthrophica,
25 arthritis infectiosa, arthritis rheumatica, different forms of arthrosis, skin burning by sun, other irradiations, chemicals or heat sources.

In all these and other cases pain and/or itching may very often be difficult to treat. Moreover,
30 oral pain killers may have undesired side effects due to their systemic mode of action, especially when taken over a prolonged period of time. Itching in itself can be very inconvenient and scratching can deteriorate the condition.

It is therefore desirable and thus the object of the invention to provide a means for topically treating itching and local pain.

This object was achieved according to the invention when it was found that glucosamine and derivatives thereof when applied topically are capable of controlling, reducing and also inhibiting the initiation of itching and pain caused by a whole range of unrelated conditions.

10 The medicinal capacity of glucosamine after oral ingestion thereof in a limited number of diseases has been described in the literature. A pilot study of the oral use of N-acetyl-D-glucosamine as a potential treatment for patients with osteoarthritis was published
15 by Talent & Gracy (1996). The potential use of oral glucosamine for wound healing and treatment for osteoarthritis is discussed by McCarty (1994 and 1996). The use of glucosamine in non-specific inflammatory bowel diseases is documented by Aasakura et al. (1995).
20 Reichelt et al. (1994) demonstrated the efficacy and safety of intramuscular glucosamine sulfate in osteoarthritis of the knee.

 The use of glucosamine as non steroidal anti-inflammatory drug in reducing the signs and symptoms of
25 osteoarthritis and rheumatoid arthritis is documented by Spencer-Green (1993) and Setnikar (1992). The toxicity of glucosamine for tissue culture cells and the antiviral activity of glucosamine depending on the cell-type and cell-line were demonstrated by Schmidt et al. (1989) and
30 Delgadillo & Vanden Berghe (1988).

 More complicated glucosamine compounds were evaluated for use in patients with osteoarthritis of the knee. In the study by Dragani et al. (1989, 1990) heparin-glucoronil glucosaminoglycan was used in a long-
35 term study for 30 days in a 3 daily administration of the drug.

 All of these prior art documents are however concerned with oral intake of glucosamine or a derivative

thereof. Based on this systemic mode of action it could not be expected that topical application of the compound and/or its derivative(s) could have an alleviating effect on itching and pain.

5

Summary of the invention

The present invention provides for the use of glucosamine and/or its derivatives for the preparation of a therapeutical composition, for the topical treatment of
10 itching and/or pain. The effect of the mediation is an acupuncture-like effect, i.e. resulting in a very quick pain reduction.

The invention thus provides topical medicaments for the alleviation of itching and pain. It has
15 surprisingly been found that this alleviation can already take place in a very short delay of time (< 1 minute) by single topical treatment. The use of glucosamine or glucosamine derivatives for the topical treatment of indications involving pain and/or itching were never
20 described before. It is also totally new and unexpected that water-soluble compounds, such as glucosamine or glucosamine derivatives, are at all able to penetrate the skin or mucosa and act so quickly on neurons and nerve impulses causing the sensation of irritation and pain.
25 The effect is therefore called: an acupuncture-like effect.

Disclosure of the invention

The use according to the present invention
30 requires glucosamine and/or one or more monomeric glucosamine derivatives such as:

- D-glucosamine hydrochloride
- D-glucosamine sulfate
- D-glucosamine iodide or other salts of D-glucosamine
- 35 N-acetyl D-glucosamine and their salts
- Chitin hydrolysate
- Chitosane hydrolysate

Glucosamine phosphates, sulfates, or acetates and their salts

D-glucosaminic acid

N-acetyl D-glucosamine phosphates, sulfates and
5 their salts

Hydrolysates of chitin and chitosane can be obtained by chitinase.

The compounds mentioned here are preferably comprised in the therapeutical compositions (also
10 referred to herein as "topical medicament") of the invention in a concentration from 0.1% to 15% (w/w), most preferably from 1% to 10% (w/w).

Topical medicaments prepared according to the invention may further comprise other active compounds for
15 healing diseases that are accompanied by local itching or pain, such as disinfectants, antibiotics, antifungal compounds, wound healing compounds, cosmetic compounds improving the skin conditions, anti-inflammatory compounds, anti-allergic compounds, anti-rheumatic
20 compounds, anti-arthritic compounds, other pain or itching relieving compounds, etc.

According to the invention it has been found that the itching or local pain is completely removed or significantly reduced in a short delay of time of even
25 less than 1 minute for a significant period of at least more than 1 hour considered that appropriate concentrations of the drug are used. Appropriate concentrations comprise more than about 0.1% (w/w) glucosamine compound per gram cream, gel, ointment,
30 solution, etc..

All topical medicaments, prepared according to the invention, may be prepared in any conventional form or in other forms suitable for topical use on the skin or mucous membranes. These forms also include all forms with
35 sustained release compositions or pre-dispersed plasters and other forms containing an acceptable carrier for the compounds.

Cosmetic acceptable carriers and additives may include: forms of vaseline, oils, emollients, surfactants, humefactants, powders, water, preservatives, agents increasing the viscosity such as polysaccharides, polypeptides, fragrances, anti-foam agents, opacifiers, colorants, each in their amount to accomplish their typical function. The basic compositions of the various topical application forms described here are well within the reach of the skilled person.

The present invention will be further illustrated in the following examples, which are in no way intended to be limiting to the invention.

EXAMPLES

15

FORMULATION

Glucosamine or one or more of its derivatives was added in the appropriate amount to one of the following formulations. The compositions thus obtained were tested as described in the Examples. All percentages are by weight (w/w) unless otherwise indicated.

Formulation 1

Water

25

Formulation 2

Cutina MD™	: 4% (Henkel, Germany)
Lanette N™	: 3% (Henkel, Germany)
Isopropylmyristate	: 3% (Henkel, Germany)
30 Oleum Amygdalae	: 4% Ph. Eu II (Conforma, Belgium)
Glycerol	: 5% Ph. EU II (Conforma, Belgium)
Methylparahydroxybenzoate:	0.2%
35 Propylparahydroxybenzoate:	0.02%
Aqua destillata	: ad 100

Formulation 3

Lanette O™	: 8% (Henkel, Germany)
Emulgin B2-C1000™	: 4% (Henkel, Germany)
Oleum Amygdalae	: 5% Ph. Eu II (Conforma,
5	Belgium)
Lanette 16™	: 2% (Henkel, Germany)
Glycerol	: 6% Ph. Eu II (Conforma,
	Belgium)
Methylparahydroxybenzoate:	0.2%
10 Propylparahydroxybenzoate:	0.02%
Aqua destillata	: ad 100

EXAMPLE 1

A patient (female; 52 years) suffering from
15 sore throat caused by β -hemolytic streptococci was
treated with a water solution (formulation 1) of N-
acetyl-glucosamine (8% w/w). The solution was sprayed
into the mouth during 10 seconds in order to treat the
infected area. Pain relief occurred already 20 seconds
20 after application and lasted for at least 1,5 hour.

12 hours later the same patient was treated
with spray containing glucosamine HCl (9% w/w and 20%
glycerol and 10% alcohol in water). Pain relief occurred
again very quickly, 36 seconds after application and
25 lasted for at least 2 hours.

EXAMPLE 2

A patient (male; 42 years) suffering from
tendinitis caused by practicing tennis was treated with
30 formulation 2 containing glucosamine sulphate 5% (w/w).
The cream was normally applied on the skin during 2
minutes to allow the penetration. Pain relief occurred
already after 50 seconds and lasted for at least 2 hours.
After 12 hours the same patient was treated with
35 formulation 2 without glucosamine. There was no pain
relief after similar application.

EXAMPLE 3

A patient (female; 53 years) suffering from herpes simplex type I infection around the nose showing extensive fissures was treated with formulation 3 containing 3% glucosamine sulfate (w/w). Already after 30 seconds pain and itching relief occurred and lasted during 3 hours. Remarkably, most of the fissures were closed after 5 hours.

10 EXAMPLE 4

A patient (female; 53 years) suffering from pain in the knee caused by a light collision during a car accident was treated with formulation 3 containing 10% (w/w) glucosamine sulfate. Pain relief occurred after 50 seconds and lasted during 3 hours. After 3 new successive treatments every 4 hours the pain was completely gone.

EXAMPLE 5

A child (male; 8 months) suffering from diaper allergy was treated with composition 2 containing 5% (w/w) glucosamine HCl instead of other commonly used oils. After applications for 1 week (3 times a day) there was always immediate relief of itching and pains.

25 EXAMPLE 6

A patient (female; 51 years) with a tendinitis due to the practice of bowling sport was treated 2 days after the onset of pain with composition 3 containing 6% (w/w) N-acetyl D-glucosamine. Pain relief occurred 25 seconds later. After 5 successive treatments (every 2 hours) pain was completely reduced.

EXAMPLE 7

A patient with allergy for cats (male; 30 years) was confronted with a stroked cat (2 years old) in a closed room (6 m x 4 m x 3 m) during 10 minutes. 8 minutes later itching started all over the forehead and

progressed after 15 minutes to the nose (external x internal).

The patient was treated on the left side of the forehead with composition 3 and on the right side of the forehead with composition 3 containing 5% (w/w) glucosamine HCl. Itching completely disappeared after 45 seconds on the right side while there was still itching on the left side. The nose was also treated inside and outside with the active cream. Itching decreased drastically already after 50 seconds.

EXAMPLE 8

A patient (male; 17 years) with nettle rash on both hands, 10 minutes after contact with the nettle plants, was treated with composition 3 containing 6% (w/w) glucosamine sulfate on the left hand and composition 3 on the right hand.

Two seconds later the itching was drastically reduced on the left hand while no relief occurred on the right hand.

EXAMPLE 9

A patient (male; 52 years) suffering from arthritis urica, and not taking any medication, was treated with composition 2 containing 9% (w/w) glucosamine HCl all over the affected right foot by 4 successive treatments with an interval of 10 minutes. Gradually strong pain relief occurred and lasted for 4 hours.

30

EXAMPLE 10

A patient suffering from eczema (atopical) (male; 14 years) on the arm-bends was treated with composition 3 containing 8% (w/w) glucosamine HCl on the left arm and composition 3 on the right arm.

Itching decreased drastically after 15 seconds and lasted during 2 hours only on the left arm.

From the above it follows that the therapeutical compositions of the invention can be used to alleviate itching and pain which result from a variety of causes. The relief is obtained very quickly and lasts for a 5 considerable period of time.

REFERENCES

- Aasakura, H. et al., Nippon-Naika - Gekki - Zasshi
84(11):1815-20 (1995)
- Delgadillo, R.A. & Vanden Berghe, D.A., J. Pharm.
Pharmacol 40:488-493 (1988)
- Dragani, L. et al., Minerva Med. 80(4):397-403 (1989)
- Dragani, L. et al., Riv. Fur. Sci. Med. Farmacol. 12:283-
295 (1990)
- McCarty, M.F., Med. Hypotheses 42(5):323-327 (1994)
- McCarty, M.F., Med. Hypotheses 47(4):273-275 (1996)
- Reichelt, A. et al., Arzneimittel Forschung 44(1):75-80
(1994)
- Schmidt, R.J. et al. J. Pharm. Pharmacol 41:784-784
(1989)
- Setnikar, I., Int. J. Tissue-React. 14(5):253-261 (1992)
- Spencer-Green, G., Postgrad. Med. 93(7):129-140 (1993)
- Talent, J.M. & Gracy, R.W., Clin. Ther. 18(6):1184-1190
(1996)

CLAIM

1. Use of glucosamine and/or one or more derivatives thereof for the preparation of a therapeutical composition for the topical treatment and quick relief of itching and/or pain.

5 2. Use as claimed in claim 1, wherein glucosamine is D-glucosamine.

3. Use as claimed in claim 1 or 2, wherein the derivative is selected from the group consisting of salts of D-glucosamine, in particular D-glucosamine
10 hydrochloride, D-glucosamine sulfate, D-glucosamine iodide; N-acetyl D-glucosamine and its salts; chitin hydrolysate; chitosane hydrolysate; glucosamine phosphates, sulfates, or acetates and their salts; D-glucosaminic acid; N-acetyl D-glucosamine phosphates,
15 sulfates and their salts.

4. Use as claimed in claims 1 to 3, wherein the therapeutical composition further comprises additional therapeutical compounds for further treating the medical conditions associated with itching or local pain.

20 5. Use as claimed in claim 4, wherein the additional therapeutical compounds are one or more of the group consisting of disinfectants, antibiotics, antifungal compounds, wound healing compounds, cosmetic compounds improving the skin conditions, anti-
25 inflammatory compounds, anti-allergic compounds, anti-rheumatic compounds, anti-arthritic compounds, anti-blood coagulant compounds, other pain or itching relieving compounds.

6. Use as claimed in claims 1-5, wherein the
30 itching and/or pain is caused by inflammation, dry skin, infection by micro-organisms such as bacteria, fungi and viruses, corns, wounds, ulcers, stings, insect bites, allergic reactions, hyper proliferation of the epithelial layer, different types of treatment with chemicals,
35 affecting the skin, eczema, tendinitis, rheumatism and rheumatic affections, such as reumatalgie, reumatide,

reumatismus articulorum acutus, reumatismus articulorum chronicus, reumatismus musculorum, reumatismus nervosum, reumatismus nodosum, rheumatoid affections, different kinds of arthritis such as arthritis urica, arthritis
5 acuta, arthritis sicca, arthritis hyperthrophica, arthritis infectiosa, arthritis rheumatica, different forms of arthrosis, skin burning by sun, other irradiations, chemicals or heat sources.

7. Therapeutical composition for topical use in
10 the treatment of itching and/or local pain comprising glucosamine and/or one or more derivatives thereof together with one or more suitable excipients.

8. Therapeutical composition as claimed in claim 7, wherein glucosamine is D-glucosamine.

15 9. Therapeutical composition as claimed in claim 7 or 8, wherein the derivative is selected from the group consisting of salts of D-glucosamine, in particular D-glucosamine hydrochloride, D-glucosamine sulfate, D-glucosamine iodide; N-acetyl D-glucosamine and its salts;
20 chitin hydrolysate; chitosane hydrolysate; glucosamine phosphates, sulfates, or acetates and their salts; D-glucosaminic acid; N-acetyl D-glucosamine phosphates, sulfates and their salts.

10. Therapeutical composition as claimed in
25 claims 7-9 further comprising one or more additional therapeutical compounds selected from the group consisting of disinfectants, antibiotics, antifungal compounds, wound healing compounds, cosmetic compounds improving the skin conditions, anti-inflammatory
30 compounds, anti-allergic compounds, anti-rheumatic compounds, anti-arthritic compounds, other pain or itching relieving compounds.

11. Therapeutical composition as claimed in claims 7-10, wherein the suitable excipient(s) is/are
35 selected from the group consisting of therapeutically and/or cosmetically acceptable carriers and additives, in particular forms of vaseline, oils, emollients, surfactants, humefactants, powders, water, preservatives,

agents increasing the viscosity, in particular polysaccharides, polypeptides, fragrances, anti-foam agents, opacifiers, colorants.

12. Therapeutical composition as claimed in
5 claims 7-11 which takes the form of a gel, cream, ointment, spray, milk, powder, liposomal, nanosomal preparations.

13. Therapeutical composition as claimed in
claims 7-12 for use in the treatment of itching and/or
10 pain associated with inflammation, dry skin, infection by micro-organisms such as bacteria, fungi and viruses, corns, wounds, ulcers, stings, insect bites, allergic reactions, hyper proliferation of the epithelial layer, different types of treatment with chemicals, affecting
15 the skin, eczema, tendinitis, rheumatism and rheumatic affections, such as reumatologie, reumatide, reumatismus articulorum acutus, reumatismus articulorum chronicus, reumatismus musculorum, reumatismus nervosum, reumatismus nodosum, rheumatoid affections, different kinds of
20 arthritis such as arthritis urica, arthritis acuta, arthritis sicca, arthritis hyperthrophica, arthritis infectiosa, arthritis rheumatica, different forms of arthrosis, skin burning by sun, other irradiations, chemicals or heat sources.

25 14. Method for preparing a therapeutical composition as claimed in claims 7-13, comprising combining glucosamine and/or one or more of its derivatives in a therapeutically effective amount with one or more excipients.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/03175

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 9214 Derwent Publications Ltd., London, GB; AN 92-110815 XP002078344 & JP 04 054126 A (MORI), 21 February 1992 see abstract	1-14
X	EP 0 281 812 A (MILOR SCIENTIFIC) 14 September 1988 see claims	7-14
X	US 4 772 591 A (MEISNER) 20 September 1988 see the whole document	7-14



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

22 September 1998

Date of mailing of the international search report

01/10/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Klaver, T

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/03175

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 281812 A	14-09-1988	AU 609090 B	26-04-1991
		AU 1193288 A	25-08-1988
US 4772591 A	20-09-1988	US 4647453 A	03-03-1987
		AU 573160 B	26-05-1988
		AU 4870285 A	24-04-1986
		CA 1261263 A	26-09-1989
		DE 3585981 A	11-06-1992
		EP 0178602 A	23-04-1986
		JP 1924661 C	25-04-1995
		JP 6051626 B	06-07-1994
		JP 61097221 A	15-05-1986